

REMARKS

In this paper, claim 7 is amended, and new claims 15 and 16 are added.

Support for the amendment to claim 7 can be found throughout the specification including the claims as originally presented, for example, at line 19 of page 26 through line 4 of page 27 of the as-filed application.

Support for new claim 15 can be found throughout the specification, for example, at line 31 of page 29 through line 7 of page 30.

Support for the new claim 16 can be found throughout the specification, for example, at lines 23-27 of page 16.

No new matter has been added.

Upon entry of this amendment, claims 1-8 and 11-16 are pending, while claims 7, 8, 15, and 16 are under examination on the merits, and claims 1-6 and 11-14 stand withdrawn.

Amendment to or cancellation of any claim herein is not to be construed as acquiescence to any of the rejections/objections set forth in the Office Action, and was done solely to expedite prosecution of the application.

Applicant respectfully reserves the right to pursue any non-elected, withdrawn, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

Claim Rejection under 35 U.S.C. §103(a)

Claims 7 and 8 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Haruta *et al.* (Nat Neurosc 4: 1163-1164, 2001; hereinafter "Haruta") in view of Tropepe *et al.* (Sc. 287:2032-2036, 2000; hereinafter "Tropepe") and in further view of Kosaka *et al.* (Exp Cell Res 245: 245-251, 1998; hereinafter "Kosaka"). The Office asserts that "Haruta et al teach that ciliary margin cells can differentiate to rod photoreceptors (that would inherently be rhodopsin positive) subsequent to formation of spherical colonies along with an explicit suggestion that such cells can be cultured to

obtain spheres or spherical colonies to induce differentiation to rod photoreceptors without gene transfer” and that “Tropepe teaches the proliferation of mouse pigmented ciliary margin cells to form spherical colonies” (pages 4 and 5 of the Office Action). The Office acknowledges that the iris pigmented epithelial cells of the present claims differ from the ciliary margin cells disclosed in Haruta and Tropepe. The Office nevertheless asserts that the present claims are *prima facie* obvious in view of Haruta, Tropepe and Kosaka (which allegedly teaches the specifics of the culture medium recited in the instant claims), because, according to the Office Action, “the skilled artisan would thus be motivated to try differentiating without a gene transfer” and that “[t]he combination of the above references proves that the knowledge and expertise for the claimed method was known in the art and the results were expected to be successful” (see pages 4 and 6 of the Office Action). Applicant respectfully disagrees and hereby traverses the rejection.

To make a *prima facie* case of obviousness, the Examiner “must step backward in time and into the shoes worn by the hypothetical ‘person of ordinary skill in the art’ when the invention was unknown and just before it was made.” M.P.E.P § 2142. This is important as “impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art.” *Id.* Three criteria may be helpful in determining whether claimed subject matter is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int’l Co. v. Teleflex, Inc.* 550 U.S. 398 (2007). With regard to the first criterion, “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143. A rationale to support a *prima facie* obviousness rejection is “that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than **predictable results** to one of ordinary skill in the art.” *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398.

Applicant submits that the combination of Haruta, Tropepe, and Kosaka does not teach or suggest the presently claimed subject matter. Although the Office states that Haruta teaches that the single pigmented ciliary margin cells can differentiate *in vitro* to rod photoreceptors subsequent to formation of spherical colonies, Haruta indicates that single pigmented iris cells (as recited in the pending claims) cannot proliferate to form spherical colonies that may further differentiate into rod photoreceptors (see Haruta at page 1163, right column, last paragraph). Applicant further notes that Haruta throughout its disclosure emphasizes the crucial rule that a gene transfer (i.e., of *Crx* gene) plays in photoreceptor differentiation of the iris-derived cells. Moreover, Haruta does not teach any method that may be employed in obtaining spherical colonies of the ciliary margin cells nor iris-derived cells. Accordingly, Applicant submits again that Haruta **merely** presents a **speculation** (with nothing more) on the possibility of differentiation of the iris-derived cells into the rod photoreceptors subsequent to spherical colony formation, **if** spherical colonies of iris-derived cells could be formed, which Haruta implies could not be done (see, e.g., Haruta at page 1164, left column, first paragraph: “**If** the iris-derived cells **could** be cultured to yield spherical colonies ...” (emphasis supplied).

Applicant submits that Tropepe does not make up for any deficiencies of Haruta. Tropepe does not teach any method of differentiating iris-derived cells into rod photoreceptors subsequent to spherical colony formation without a gene transfer. Tropepe only teaches proliferation of a different type of cells (i.e., mouse pigmented ciliary margin cells) to spherical colonies. Applicant submits and the Office appears to concede that pigmented ciliary margin cells in Tropepe are a different type of cells from the iris pigmented epithelial cells recited in the pending claims. While the Office states that “it is well known that the iris and ciliary cells can behave similarly under similar culture conditions”, this statement is belied by Tropepe, which specifically teaches that ciliary margin cells, but **not iris-derived cells**, formed spherical colonies under the conditions disclosed in Tropepe. Applicant further notes that Kosaka only teaches the specifics of the culture medium, and nothing more. Accordingly, Applicant contends that the combination of Haruta, Tropepe, and Kosaka does not teach or suggest each and every element of the present claims (e.g., inducing differentiation of the iris-pigmented epithelial cells into the rhodopsin-positive retinal nerve cells without a gene transfer).

Applicant contends that a skilled artisan would not be motivated to combine the teachings of Haruta, Tropepe and Kosaka as suggested in the Office Action, and would not have had a reasonable expectation of success in making such a combination at the time the present invention was made. Rather than providing any motivation or suggestion on differentiating the iris-derived cells into spherical colonies, Tropepe teaches something opposite: Tropepe reported that sphere colonies **could not** be obtained from the iris-derived cells of an adult rat (*see*, e.g., Tropepe at page 2033, first column, second paragraph). Tropepe thus teaches that iris-derived cells do not form spherical colonies, and Tropepe therefore teaches away from the presently-claimed subject matter.

However, the Office has asserted that “Tropepe is teaching away is also not relevant” (*see* page 5 of the Office Action). Such an assertion is improper. According to MPEP 2144, teaching-away evidence is relevant in a *prima facie* case of obviousness, by stating that the obviousness “may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.” *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). Here, Applicant contends that Tropepe’s teaching way is highly relevant, as a skilled artisan would not be motivated to combine Tropepe and Haruta **for the purpose** to arrive at this invention, particularly in view of Tropepe’s failure report on developing the *iris-derived cells* into spherical colonies.

Even *assuming* that, *arguendo*, one skilled in the art were to combine the cited references as suggested by the Office, there would be no reasonable expectation of success to reach the claimed subject matter. To make a *prima facie* case of obviousness, “a reasonable expectation of success is required”, i.e., that the combination “would have yielded nothing more than predictable results to one of ordinary skill in the art.” MPEP 2143.02 (citing *KSR v. Teleflex*, 550 US 398).

In order to reach its conclusion that there was a reasonable expectation of success, the Office has made an *assumption* that “the iris and ciliary derived cells can behave similarly under similar culture conditions” (*see* pages 4 and 6 of the Office Action). Applicant contends that such an assumption is unfounded and is completely against the clear teachings presented in Tropepe and Haruta. Tropepe expressly

teaches that the iris and ciliary derived cells behave **dissimilarly**, by presenting the research results that the *ciliary margin cells* can successfully differentiate into spherical colonies, while the *iris-derived cells* **did not** (see, Tropepe at page 2033, first column). Haruta indicates that the *pigmented ciliary margin cells* and the *iris pigmented epithelial cells* would behave differently, by stating that “the *single pigmented ciliary margin cells*, but not *single pigmented iris cells*, can differentiate *in vitro* to form spherical colonies of cells that can differentiate into rod photoreceptors” (see Haruta at page 1163). Clearly, the teachings in Tropepe and Haruta do not support, and in fact contradict with, the Office’s assertion that “the iris and ciliary derived cells can behave similarly under similar culture conditions”.

Considering the cited references in their entirety, a skilled artisan would understand that Haruta presents no more than a speculation or *wishful thinking* on the possibility of differentiating the iris-derived cells into photoreceptors subsequent to spherical colony formation without a gene transfer, and that the combination of Tropepe, Haruta and Kosaka would fail in achieving its intended purpose.

Although the Office acknowledges that Tropepe teaches spherical colony formation of pigmented ciliary margin cells (not the iris pigmented epithelial cells of this invention), the Office alleges that differentiating the iris-derived cells into spherical colonies could be done by “tak[ing] into account only knowledge which was within the level of ordinary skill in the art” (see page 5 of the Office Action). Applicant strongly disagrees. None of the references relied upon by the Office (Haruta, Tropepe and Kosaka) discloses that iris-derived cells can form spherical colonies. Both of Haruta and Tropepe indicate that iris-derived cells do not form spherical colonies, even if ciliary margin cells do form spherical colonies. None of the references relied upon by the Office discloses that conditions are known or can be found that would result in formation of spherical colonies of iris-derived cells. In view of such, one skilled in the art would conclude that, at the time of the invention, it was not clear in the art whether (or how) *iris-derived cells* could actually differentiate to form spherical colonies without a gene transfer. Indeed, in view of Tropepe’s failure report, one would reasonably expect that *the iris-derived cells cannot* differentiate to form spherical colonies without a gene transfer. It is not enough for the Office to simply state that “the

knowledge and expertise for the claimed method was known in the art and the results were expected to be successful” (Office Action at page 6), when the cited references point to the opposite conclusion. Accordingly, Applicant submits that there would be *no* reasonable expectation of success in the art to arrive at this invention, even *if* one were to combine and modify the teachings in Haruta, Tropepe, and Kosaka.

Therefore, Applicant submits that the Examiner has failed to make a *prima facie* case of obviousness, for at least the following reasons: first, the combination fails to teach each and every element of the claimed subject matter; second, one skilled in the art would not be motivated to combine then modify the cited references as suggested in the Office Action; and third, even *if* such motivation to combine did exist, there would be no reasonable expectation of success in making such a combination. Accordingly, the claimed subject matter is patentable over Haruta, Tropepe, and Kosaka.

Applicant additionally notes that the pending claims now further recite steps of selectively culturing the isolated iris pigmented epithelial cells by a floated coagulated mass culturing technique, and of performing adherent culturing of the iris pigmented epithelial cells with a serum-free culture medium (with certain specifics, e.g., as recited in the pending claims) to induce differentiation of the iris pigmented epithelial cells into the rhodopsin-positive retinal nerve cells, wherein the iris pigmented epithelial cells *are obtained in the selectively-culturing step* and have not been subjected to a gene transfer (*see*, e.g., claim 7 for details). Applicant submits that the cited references do not teach or suggest each and every element of the claimed subject matter, and that the pending claims are clearly patentable over Haruta, Tropepe, and Kosaka.

Therefore, reconsideration then withdrawal of the rejection under 35 U.S.C. § 103(a) over Haruta and Tropepe in view of Kosaka is proper and the same is requested.

CONCLUSION

In view of the remarks made herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney.

Although it is not believed that any further fee is needed to consider this submission, the Office is hereby authorized to charge our deposit account **04-1105** under Order No. 64603 (70904), should such fee be deemed necessary.

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Respectfully submitted,

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